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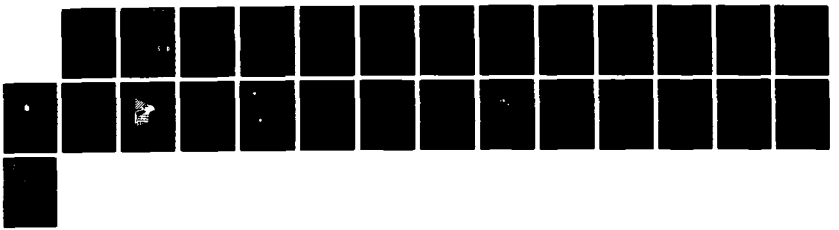

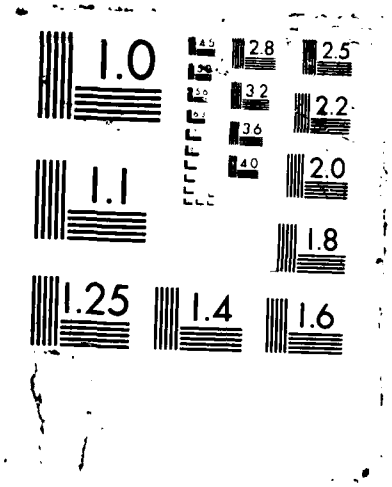
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The Effect of an Experimental Missile Wound to the Brain on Brain Electrolytes, Regional Cerebral Blood Flow and Blood Brain Barrier Permeability

Annual Summary Report

Michael E. Carey, M.D.

September 15, 1984

Supported by

U.S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701-5012
Contract No. DAMD17-83-C-3145

Louisiana State University Medical Center
1542 Tulane Avenue
New Orleans, Louisiana 70112

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SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION: Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release; distribution unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: Louisiana State University; 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code): New Orleans, Louisiana 70112	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Research & Development Command; 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: Contract No. DAMD17-83-C-3145
8c. ADDRESS (City, State, and ZIP Code): Fort Detrick, Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
61102A	3M1-61102BS10	BA	277

11. TITLE (Include Security Classification): The Effect of an Experimental Missile Wound to the Brain on Brain Electrolytes, Regional Cerebral Blood Flow and Blood Brain Barrier Permeability

12. PERSONAL AUTHOR(S): Carey, Michael E.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Annual	FROM 83/7/1 TO 84/6/30	84 September 15	

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
06	16		brain wounding, blood-brain barrier, brain water and electrolytes
06	21		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

We have developed an experimental gun to inflict a precise transcranial missile wound to the brain of a cat. The missile is a 30 mg steel sphere which optimally deposits 1.3 Joules of energy in the right cerebral hemisphere. After wounding, a breakdown of the blood-brain barrier occurs and alterations of the brain water sodium and potassium are seen. Immediately after missile impact arterial hypertension and bradycardia ensue. Respiratory abnormalities also occur. Wounds of 1.8 Joules or greater cause immediate respiratory arrest and sometimes cause brain stem hemorrhages.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
Mrs. Virginia Miller	(301) 663-7325	SGRD-RMI-S

DD Form 1473, JUN 86 — Previous editions are obsolete. — SECURITY CLASSIFICATION OF THIS PAGE

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Summary

Of all combat fatalities since WW2 almost half have resulted from brain wounds. The postoperative neurosurgical mortality has remained between 10% and 20% since WW2. Up to one third of those surviving brain wounds are able to return to some form of Army duty. Despite the importance of brain wounding as a source of combat mortality and morbidity, there have been few systematic studies of brain physiology after wounding that might lead to a better understanding of altered cellular physiology after such trauma and an amelioration of the effects of wounding.

In major wars most brain wounds (70% to 80%) are caused by fragments rather than bullets. In this project we make a uniform, right cerebral, anterior-to-posterior brain lesion in the cat using a 30-mg steel sphere fired from a gun to simulate a fragment wound to the brain.

Structural brain damage from trauma results in breakdown of the blood-brain barrier and changes in brain water and electrolytes. Breakdown of the blood-brain barrier with passage of water into the brain parenchyma leads to cerebral swelling and increased intracranial pressure. Because this breakdown may be a danger to the brain-wounded soldier, we are examining brain water and brain potassium and sodium concentrations after wounding. Six hours after injury, cats have shown both increases and decreases in brain water from - 15% to +15%) in areas surrounding the missile wound as compared with control values. Brain K^+ and Na^+ in our normal cats were 95.0 mEq/L and 54.0mEq/L respectively. After wounding, brain K^+ changes have ranged from -17& to +20% and brain Na^+ changes were from -27% to +16% in brain areas surrounding the wound. In further experiments we will more precisely delineate changes in these important variables.

We also have observed significant brain stem effects consequent to wounding. Immediately after wounding systemic arterial hypertension (sympathetic effect) and bradycardia (parasympathetic effect) usually occur. With lower-energy wounds no respiratory effect was noted; with intermediate-energy wounds transient apnea occurred; with higher-energy wounds permanent respiratory arrest was seen in conjunction with frank brain stem hemorrhage. Whether any of these physiological effects can be reduced by drug therapy has yet to be determined.

Foreword

In conducting the research described in this report, the investigators adhered to the Guide for the Care and Use of Laboratory Animals prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, revised 1978).

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BACKGROUND: Perusal of combat medical statistics consistently shows that brain wounds from missiles account for almost half of all combat fatalities.(1,2) The extreme vulnerability of the brain can be seen when it is realized that the head accounts for only 9% to 12% of exposed body area in combat.(3) Despite this fact there have been relatively few studies to understand the physiological effects of a missile on the brain. Perhaps people have been fatalistic about those with brain wounds, believing that they were "lost" not only to life but to the Army in particular. We agree that bullet wounds to the brain are generally fatal. In major combat operations, however, more than 70% of wounds are inflicted by fragments (4) and not all fragment wounds to the brain are lethal. Furthermore, the postoperative mortality of a fragment wound to the brain is only 10% to 20%(5,6,7,) and up to one third of those who were operated on for a brain wound in WW2(8) and Vietnam(9) were able to continue in some form of Army duty. Improving brain function after wounding, therefore, may lessen morality and increase the numbers of brain-wounded available for continued Army duty.

The most recent series of experiments on brain wounding has been undertaken by Crockard and associates(10-17), who inflicted brain wounds on chimpanzees through trephine openings in their skulls. They found good correlation between missile energy and physiological effects. After brain wounding, the respiratory pattern changed but arterial blood gases did not. The mean blood pressure fell, then rose, whereas the intracranial pressure rose, then fell. The cerebral perfusion pressure fell about 50% cerebrovascular resistance increased, and cerebral blood flow decreased concomitantly.

Although many of these observations are informative, the experiments had relatively little focus on brain physiology per se. Furthermore, the brain wounds so created were made by an unrealistically large missile (310mg) through an already trephined skull. This circumstance, too, is highly unrealistic and would tend to attenuate the effect of any overpressures in the brain caused by the kinetic energy deposit of the missile.

Our ballistics experiments are intended to study the effects of a brain missile wound created by a simulated fragment, specifically to examine traditional physiological factors that have been looked at in other brain trauma models: brain edema, cerebral blood flow and blood flow autoregulation, blood-brain barrier (BBB) integrity, the coupling of blood flow and brain metabolism, and changes in neurotransmitters and other brain amines. We wish not only to described physiological perturbations caused by the missile but to see whether any observed derangements can be lessened by means of specific drug treatment.

Experimental Gun: Crucial to our program is a gun capable of firing a 30-mg steel sphere at several hundred meters per second (mps) through the intact skull to make the brain wound. Before undertaking this project we discussed this requirement with Mr. Robert Carpenter, formerly of the Edgewood Arsenal, who had made several similar devices for the Arsenal in the past. Mr. Carpenter indicated that he could make a helium-driven gun that could fire a 1.98-mm, 30-mg steel sphere at the requisite velocity. It should be stressed that from the outset that Mr. Carpenter said he had

made several instruments to fire larger spheres but had never made a device to fire such a small missile and that our helium gun would be "unique."

As provided to the project by Mr. Carpenter, the instrument had the necessary velocity but was very inaccurate owing to the use of irregular, grossly oversized, commercially available, stainless steel tubing as a barrel liner. Furthermore, these barrel liners were held in place by 4 set screws that tended to warp the liners. We attempted to create wounds with those barrel liners from the end of March until the end of May 1984. We resorted to using a collimating device to deflect widely inaccurate shots but this proved exasperating and exhausting because of the many shots (10-12) and time (2 to 4 hours) needed to make a satisfactory brain wound. By May it was evident that a better barrel system was necessary. Mr. Carpenter has now provided an entirely redesigned barrel using specially remilled, guaranteed straight, barrel liners precisely 0.002 inches oversize relative to our test missile. The new barrel and barrel liners arrived on or about 10 August 1984.

Initially, the helium gun provided by Mr. Carpenter had a good correlation between pounds shooting pressure and missile velocity. After 100 and 200 shots, however, linearity between pressure and velocity lessened and repeat tests showed no statistical differences between missile velocity overlap between the two pressures. By August 1984, the helium charge release valve had worn out and had to be modified.

Timing Mechanism: In our system, missile velocity is determined by the time between break screens set at a known distance. The original chronograph supplied for this purpose by Mr. Carpenter was erratic. We have substituted a crystal oscillator timer that is now giving excellent timing results. We now precisely know the velocity (and energy) of the fired missiles.

Experimental Animal: We selected the cat as the experimental animal because the mongrel cat's head is much more standard than the mongrel dog's. The position of the cat's head in the stereotaxic frame, thus, will be more uniform allowing more standard wound placement from animal to animal. The cat also has ample cerebral white matter (where brain edema develops). Importantly, the cat has been used in other experiments on brain injury (18,19) and circulation studies. (20,21) The cat is relatively small and inexpensive; its smaller size makes the anticipated per kilogram isotope doses less costly.

In our original proposal we indicated that we would make a transverse wound injuring both frontal lobes. We have since concluded that a front-to-back wound of one cerebral hemisphere would be preferable: one hemisphere will sustain direct missile trauma while the other will not. Frontal, anterior-to-posterior wounds are common in combat and, hence, our revised "standard missile trajectory" is more realistic.

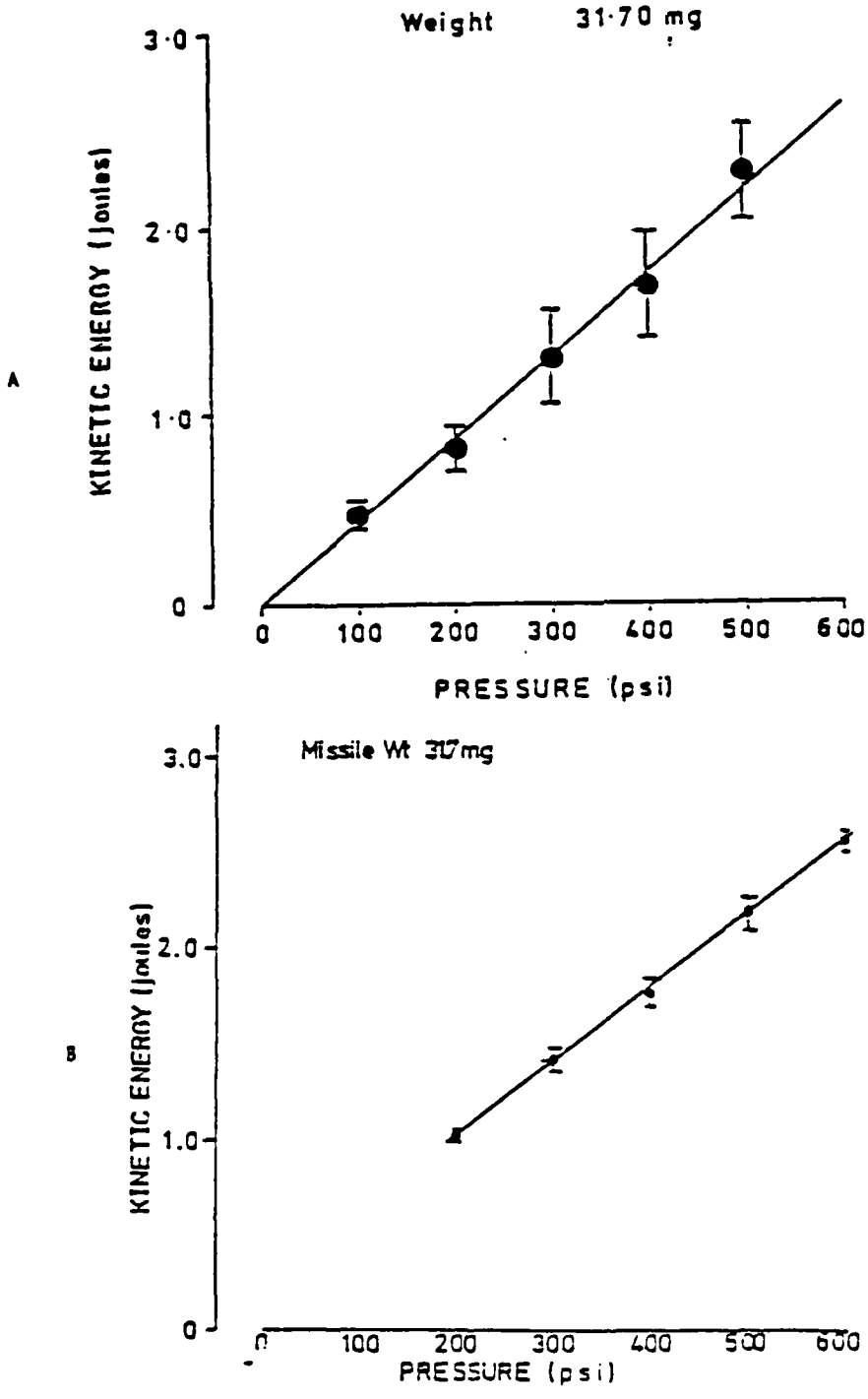
RESULTS:

A. Gun:

By a major redesign of the gun, including a new barrel, precision-

made barrel liners, a completely new solenoid valve, new valve release mechanism, and new timer, we now have a precision wounding instrument. It is accurate within 2 to 3 mm at 80 cm. With the modified gun, missile velocity and kinetic energy are close functions of pressure from 200 to 600 pounds shooting pressure (Figure 1). We have also attached a laser aimer that greatly speeds up aiming the gun.

Figure 1: Kinetic Energy vs Shooting Pressure



Kinetic energy of missile vs. pounds shooting pressure; means ± S.D. values obtained from a gun as originally provided (A) had quite large S.Ds. which preclude statistical significance between any two sequential points from 300 to 600 pounds pressure. (B) is same plot with modified gun. S.Ds. much reduced. KEs associated with any two shooting pressures are statistically different. Each point obtained from 5-6 shots.

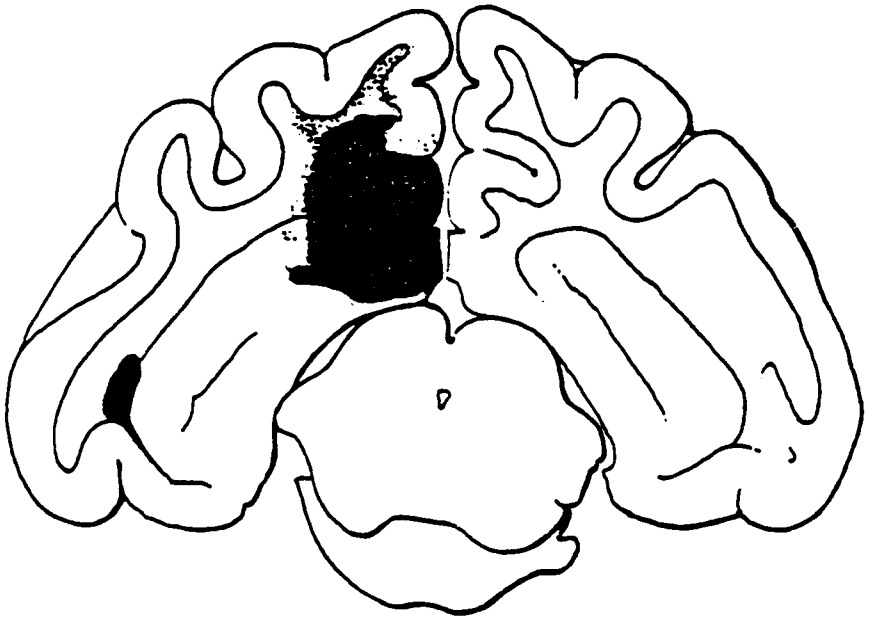
B. The Cat:

Since we envision an in-depth study defining the physiologic effects of a missile wound and ascertaining its best treatment, we have spent considerable time working to achieve a standard brain wound of the right cerebral hemisphere that is not immediately fatal.

Our preliminary tests showed that the light, 30-mg, missile did not penetrate the intact frontal skull of the cat because it ricocheted off the sloping frontal-nasal bone. In our experiments, therefore, we surgically remove the sloping outer wall of the right frontal sinus. Bleeding is minimal. The posterior wall of the sinus (and, hence, the frontal wall of the skull) remains intact. The posterior wall of the frontal sinus (frontal wall of the skull) is virtually at right angles to the missile trajectory and with a normal impact the missile in capable of penetrating the skull and entering the brain.

When we fire the 30-mg sphere at 226 mps (0.81 Joules), it usually fails to defeat the skull. When we fire at 325 mps (1.4 Joules) the missile penetrates the skull and brain, and about half of the cats die. This kinetic energy represents our LD_{50} energy. When fired at 430 mps (2.6 Joules), the deposited energy affects the brain stem and causes an immediate respiratory arrest. This represents a fatal wound. We have, therefore, determined that to create a nonfatal brain wound we will have to work through a fairly narrow energy "window": missile kinetic energy will have to be between 0.9 and 1.4 Joules. Figure 2 depicts a "standard" brain wound of the cat's right cerebral hemisphere.

Figure 2: Brain Section Showing Missile Track



Brain section shows the missile track filled with blood in the medial aspect of the right hemisphere. Stippling shows penetration of Evans blue dye into brain parenchyma indicating breakdown of blood-brain barrier. This animal was sacrificed six hours after wounding. A small amount of blood is in the temporal horn of the right lateral ventricle.

Not only must the brain wound be made in a standard way but tissue sampling throughout the brain must be uniform as well. Uniformity of sampling will be absolutely critical when comparing physiological effects between treated an nontreated cats. To ensure uniformity of brain samples Gurcharan Sarna, PhD, who has joined this project, has developed a unique wax-imprint, brain-mold system that allows each cat's brain to be positioned at a precise angle to a series of cutting blades. This allows all cat's brains to be sectioned into eight 5-mm thick slices that have the same orientation as those brain slices depicted in a standard cat stereotaxic atlas. We sample up to 60 areas for each brain and have carefully determined which cerebral hemisphere tissue samples represent gray matter, which are composed of white matter, and which are mixed gray and white. Tissue sampling is precise and uniform for each animal. Figure 3 depicts the sampling protocol for one brain slice.

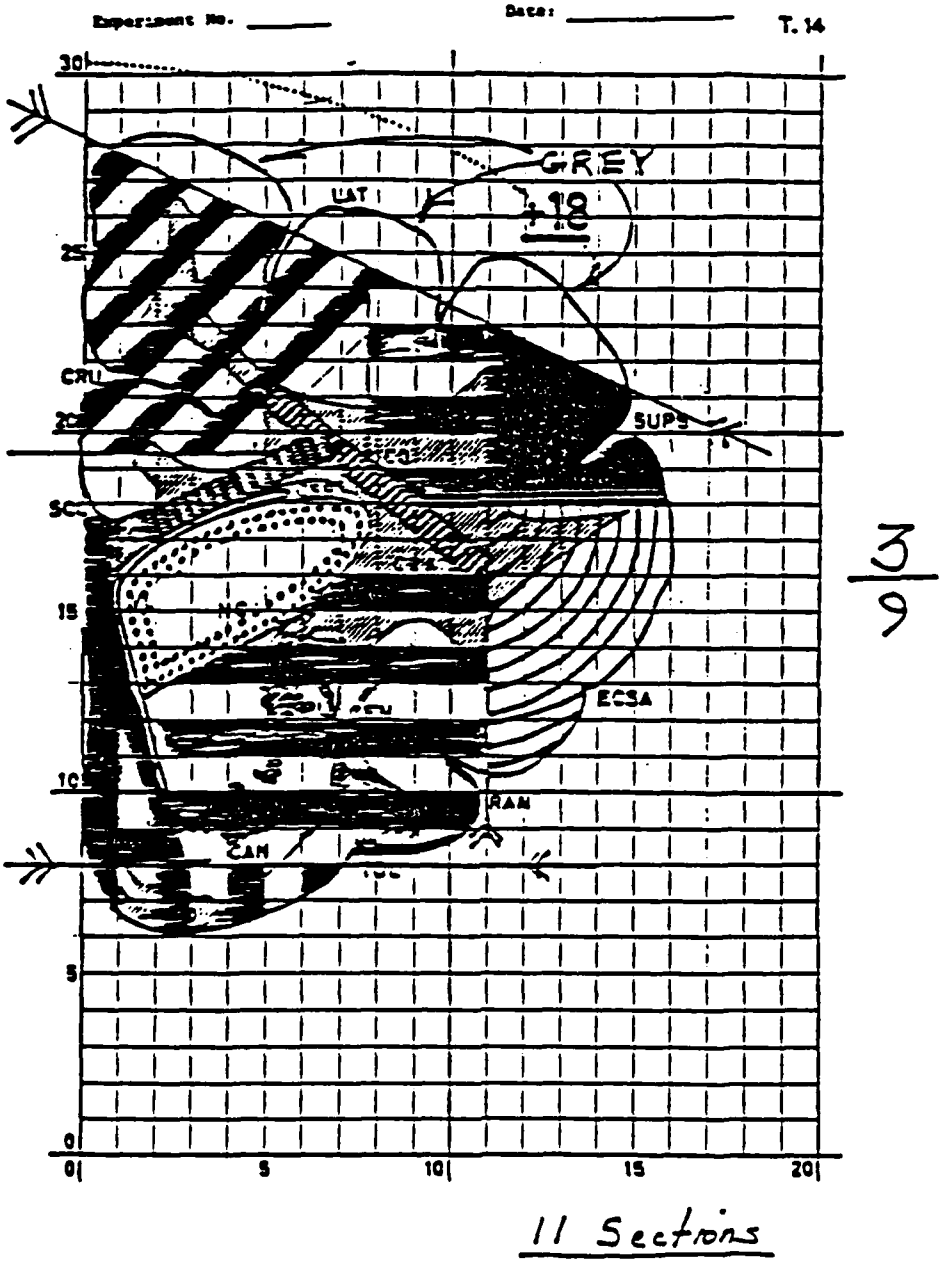
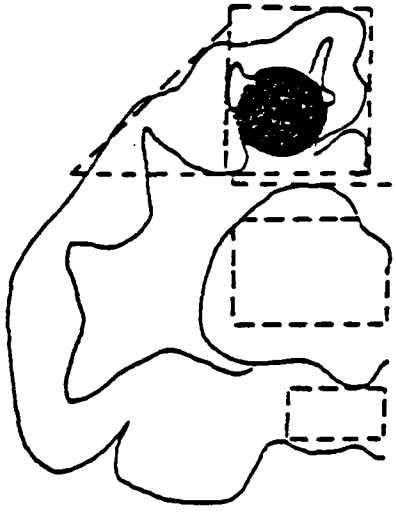


Figure 3: Proposed Tissue Sampling Scheme for one Brain Slice

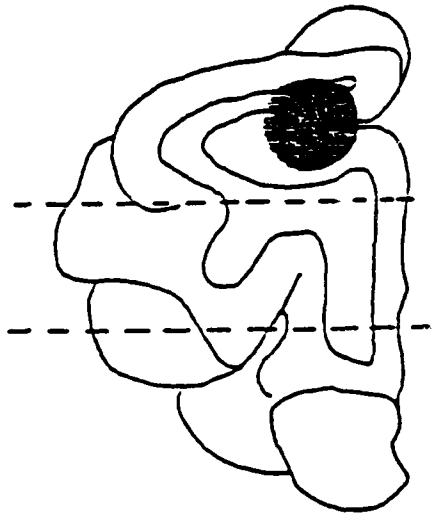
C. Physiological Results:

1. Brain Water and Electrolytes: Intact brain contains about 78% water, and in normal brain tissue there are about 95 mEq/L of potassium and 55 mEq/L of sodium ($K^+/Na^+ = 1.73$) (23) Traumatic brain injury that destroys the integrity of the blood-brain barrier (BBB) causes an alteration in the levels of brain water and electrolytes.

Brain water in our control cats ranges from 74.43 to 78.41 mEq/L 100g whereas brain-tissue potassium averages 95.03 mEq/L and brain-tissue sodium 53.95 mEq/L. Figure 4 shows an example of the percentage changes in water and electrolytes in one cat six hours after wounding. Areas of both swelling and shrinkage distal to the wound are apparent. Although the absolute concentration of of Na^+ and K^+ changed, the ratio of K^+ to Na did not. (These are preliminary findings.)



	H_2O	Na	K
Cortex (around wound)	+0.4	+2.5	-5.5
Cortex (side of wound)	-9.7	+3.8	+1.0
Corpus Callosum	+16.3	+7.1	+4.2
Thalamus	+15.8	+14.1	+19.5
Hypothalamus	-1.2	+0.9	-1.2

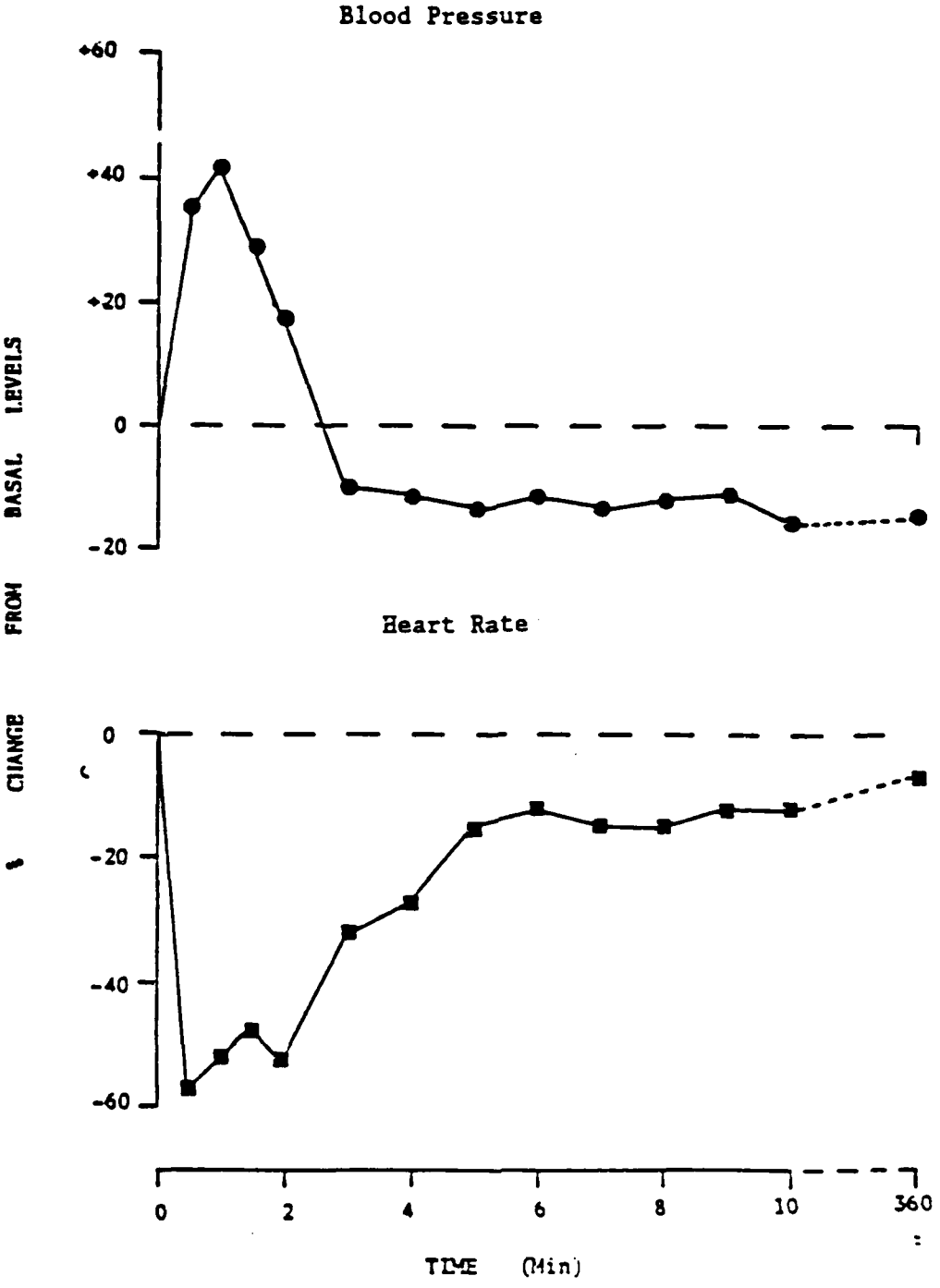


H_2O	Na	K
+2.47	+1.00	+4.8
+2.04	+10.10	+2.68
-14.74	-27.61	-17.14

Figure 4: Two brain sections showing altered water and electrolytes about a missle wound. (The missle track is represented by the round black circle.)

2. Vasomotor Changes: Penetration of the brain by the missile with its concomitant deposit of energy often causes severe vasomotor changes,, presumably because of an effect on the brain stem. We have observed several patterns, but the most common one after wounding is an immediate increase in blood pressure (sympathetic effect) along with bradycardia (parasympathetic effect), which occur together and last up to 10 minutes. After 10 minutes, both pulse and BP tend to return to baseline levels (Figure 5).

Figure 5: Mean Arterial Blood Pressure and Heart Rate After Wounding



Profound autonomic disturbances are seen following a missile wound of the right cerebral hemisphere.

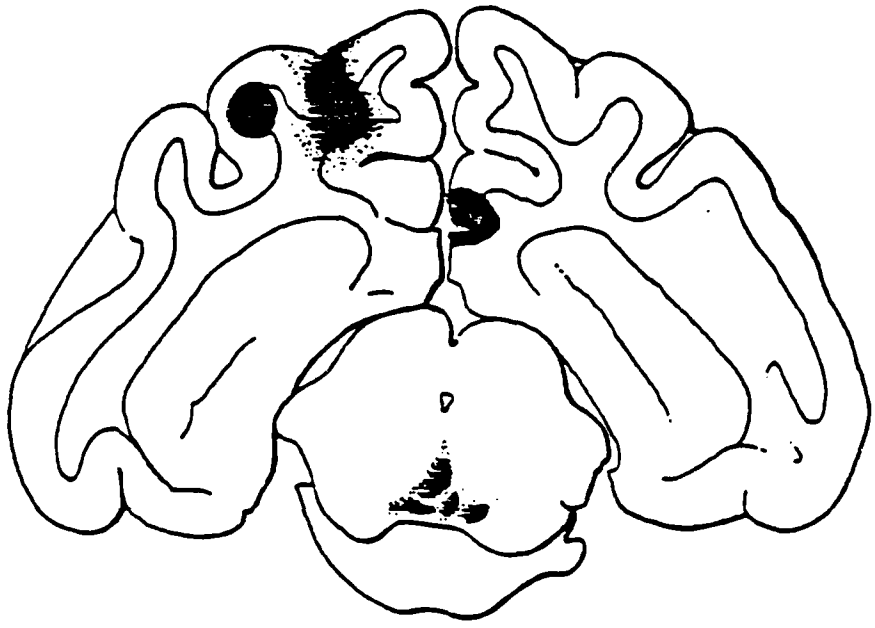
3. Respiratory Effects: As mentioned above, missile energy deposit of 2.6 Joules or greater caused instantaneous and permanent respiratory arrest; 1.4 Joules caused temporary loss of respiratory effort in about half of the animals, whereas energy deposits of 0.9 Joules caused no or minimal respiratory abnormalities.

4. Pathologic Findings: Control brains have shown no alterations in morphology or BBB permeability even after the cats were on the respirator for 6 hours. While animals are on the respirator we monitor arterial blood gases and end expiratory CO_2 levels. Integrity of the BBB is tested by the intravenous injection of 2% Evans blue dye (MW 69,000) 20 to 30 minutes before the animal is killed. The BBB is considered intact if no leakage of blue dye is evident anywhere in the brain.

At this point we have studied brain morphology in 10 missile-wounded cats some of whom have received lethal (>2.6 Joules) brain wounds. Naturally, all brain-wounded cats show a missile track extending from the right frontal lobe to the region of the right occipital lobe. The amount of blood filling each missile track varies. Around the missile track, particularly in the white matter, there is a 1 to 2 mm zone stained by Evans blue dye, indicating a gross breakdown in the BBB caused by the missile (figure 2). Some of the white matter about the brain appears swollen. Blood is widely present in the subarachnoid space over the ipsilateral hemisphere. Evidently the brain is damaged at a distance from the main missile track as well because in several animals small intraparenchymal hemorrhages are evident in the ipsilateral thalamus and in the contralateral hemisphere.

Of special significance is the observation that high-energy (>2.6 Joules) cerebral hemisphere wounds that cause permanent respiratory arrest are associated with brain stem hemorrhages (Duret's lesions) (Figure 6). Nonfatal missile wounds, although causing profound cardiovascular effects, do not cause prolonged respiratory alterations and are not associated with gross hemorrhage within the pontomedullary area.

Figure 6: Hemispheral and Brain Stem Hemorrhages Following a Missile Wound



This fatally wounded cat was shot with 2.6 Joules. This relatively small missile track is in the right hemisphere. Note the small area of damage in the contralateral hemisphere. Note especially the brain stem hemorrhages causing permanent respiratory paralysis.

DISCUSSION: To create a standard missile wound to the brain, a reliable gun is necessary. Commercially available air guns fire a 300 to 400 mg pellet, far too large for even human studies simulating a typical wound-producing fragment. WDMET data from Vietnam indicate that the weight of the usual fragment causing a fatal brain wound was 110 mg.(24) In our studies on cats we are using a 30-mg steel sphere, still somewhat large, but the smallest practicable. No commercial gun capable of delivering so small a sphere at the requisite velocities exists. Mr. Robert Carpenter, formerly an experimental gun designer for ballistics testing at the Edgewood Arsenal, designed a unique helium-powered gun for our small missile. It would have been unrealistic to expect so unique an instrument to work perfectly from inception. Three major problems have been encountered with this new gun: erratic aim, inability to time the break screens properly and nonlinear helium pressure vs. missile velocity. Each of the problems has been resolved by means of a major redesign. Unfortunately, we had to wait for two months for a new barrel to be designed and fabricated and for new barrel liners to be manufactured.

Brain wounding and subsequent brain sectioning and tissue sampling have been standardized. Rigorous control is absolutely crucial if one is to compare various drug treatments for combatting brain edema and maintaining normal brain tissue electrolytes. We must be absolutely certain that the brain areas we compare are from precisely identical sites.

Our preliminary data show that 6 hours after a missile wound, BBB breakdown is evident about the missile track. The surrounding brain shows variously increased and decreased water content. The finding of both tissue swelling and shrinkage may have important ramifications in the treatment of brain wounds in that a particular protocol for reducing swelling (e.g., hyperosmolar agents) may act to the detriment of those areas that have actually lost water. Brain-tissue potassium and sodium concentrations also change. Owing to problems with gun performance (now corrected), we have not analyzed enough wounded brains to show statistical significances. We have also not done any drug testing.

The missile traversing the right cerebral hemisphere several centimeters from the brain stem causes pronounced medullary effects. No continuity of structural damage occurs from cerebral hemisphere to midbrain and pons-medulla. Documented medullary effects include increased systemic arterial pressure, bradycardia, and apnea. Thus, widespread brain stem dysfunction occurs, causing both sympathetic and parasympathetic responses as well as varying degrees of interruption of respiratory control. Higher-energy, right cerebral hemisphere wounds, in particular, are associated with permanent apnea and brain-stem hemorrhages. These destructive medullary hemorrhages obviously prevent the resumption of respirations.

Future experiments will allow us to ascertain more precisely the mechanism behind brain-stem dysfunction following the missile wound. Obviously transient increase intracranial pressure associated with missile

passage through the brain might affect brain-stem function directly. An indirect cause might also be postulated: missile wounding could seriously affect blood flow to the medulla. The transient sympathetic, parasympathetic, and respiratory dysfunctions that we have observed could result from medullary ischemia. Even the brain-stem hemorrhages that we have observed from our fatal wounds could result from a primary vascular phenomenon rather than from a direct pressure effect on the brain-stem. Blood flow autoregulation is through to be mediated by pre-arteriolar control mechanisms. (25) Energy deposit from the missile may disrupt cerebral blood flow autoregulation. With the ensuing hypertension in the face of failed autoregulation, medullary capillaries may then rupture because they are not protected from stress by functioning precapillary arterioles. Our intended studies (02 year) on regional cerebral blood flow and autoregulation of blood flow after missile wounding will help clarify this issue.

Our experiments thus far appear not only to have delineated local alterations in brain water and electroltyes about the missile wound itself but also to have identified a continuum of brain-stem effects after a missile wound: from mere transient, parasympathetic-sympathetic activity to temporary apnea, and finally to permanent respiratory arrest associated with brain-stem hemorrhage.

Special Note: Owing to the national debate on the use of experimental animals that occurred during the autumn and winter of 1983 this ballistics project was halted by DOD directive from 15 September 1983 until 19 January 1984. During this interval we were busy refurbishing and equipping our laboratory and particularly in recruiting a top-flight PhD in brain physiology, Gurcharan Sarna, to refine and manage the project on a day-to-day basis. The four-month ban on experiments, resulting uncertainties concerning permissible experimental animals, and "gear-up" time once the project was given the "go-head" resulted in our first live animal experiments being done in March 1984. Wounding experiments were once again curtailed in June and July 1984, awaiting the arrival of a more satisfactory gun barrel. They have now resumed.

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